REMARKS

Claims 1-30 are under examination in this office action. Claims 31-91 have been withdrawn as being drawn to non-elected subject matter. Claims 1-5, 9, 15, 16, 18, 19, and 28 have been amended. Applicants respectfully assert that all amendments are supported by the original disclosure and do not introduce new matter. Moreover, Applicants further respectfully assert that the amendments merely clarify the scope of the claims.

By way of review, this invention relates to antisense oligonucleotides, in particular antisense oligonucleotides complementary to the Follicle Stimulating Hormone Receptor (FSHR) gene. The compositions of the present invention can be used to block follicle stimulating hormone (FSH) action. Regulation of FSH is advantageous in the treatment of epithelial ovarian cancer, menstrual dysfunction, ovulation and fertility. The invention relates to oligonucleotides that are highly specific for FSHR in ovarian follicular granulosa cells. The oligonucleotide may contain one or more internucleosidic linkage that stabilize the structure, preventing degradation that can occur following administration.

In the subject Office Action dated December 20, 2005, the Examiner rejected pending claims 1-30 under 35 U.S.C. §112, claims 1-5 under 35 U.S.C. §102 and claims 1-12, 14-22 , and 26-29 under 35 U.S.C. §103. These rejections are addressed in full herein.

Priority

The Examiner has noted that Applicant has not complied with 35 USC §119 in that Applicant has not properly referenced the earlier filed application. Applicant has amended the specification accordingly.

Sequence Listing

The Examiner has noted that the specification comprises a sequence listing on pages 65-69 that do not start on a separate page. Subsequently, a "Sequence Listing " as required by §1.821(c)

was submitted on paper. To avoid duplication, Applicant has deleted the sequence listing on pages 65-69 to avoid duplicate sequence listings.

Claim Rejections - 35 USC § 112

The Examiner has rejected Claims 1-30 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner has rejected claim 1 as vague and indefinite, finding the metes and bounds of "a nucleotide sequence of a follicle-stimulating hormone receptor" unclear. This claim is now amended to refer to at least one antisense oligonucleotide that is complementary to a nucleotide sequence of a follicle-stimulating hormone receptor (FSHR) transcript.

The Examiner has rejected Claims 2-14 and 22-24 as vague and indefinite, finding the metes and bounds of "the antisense oligonucleotide(s)" unclear. In the original claims, Claim 1 recites that the composition comprises at least one antisense oligonucleotide while claims 2- 14, (which depend from claim 1) and claims 22-24 (that depend from claim 7) recite alternatively "the antisense oligonucleotides" and "the antisense oligonucleotide." The Examiner found the claims vague and indefinite because this language made it unclear whether the singular or plural was intended. The remaining claims have been amended and refer to the "oligonucleotide" in the singular to properly reference "at least one" oligonucleotide as claimed in independent claim 1.

The Examiner has noted that claims 4, 5 and 6 lack antecedent basis with respect to the term "antisense oligonucleotide[s]." Claims 4 and 5 have both been amended and now properly depend on claim 1, referring to "antisense oligonucleotide" in the singular. Claims 4, 5 and 6 now have proper antecedent basis.

The Examiner reads claim 2 as vague and indefinite, finding that the metes and bounds of "alpha-anomeric forms of deoxyribonucleotides and ribonucleotides" unclear. Claim 2 has been incorporated into claim 1 and the language of original claim 2 has been amended such that it should now be clear that applicant intends to claim both alpha-anomeric forms of deoxyribonucleosides and alpha-anomeric forms of ribonucleosides.

The Examiner reads claim 3 as vague and indefinite in that the metes and bounds of "a stable duplex" are unclear because the antisense oligonucleotide is said to form a duplex with the double-stranded FSHR gene instead of the single-stranded transcript. Claim 3 was also rejected on the basis of insufficient antecedent basis for the limitation "the FSHR gene." The language of original claim 3 is now incorporated into claim 1 and is currently amended to refer to a stable duplex formed with the transcript of the FSHR gene and not directly with the gene. The language has also been amended so that there is now proper antecedent basis for the acronym "FSHR", the abbreviation in parenthesis "(FSHR)" inserted following the phrase "follicle-stimulating hormone receptor" as suggested by the Examiner. Claim 3 has been amended, and no longer refers to "a stable duplex."

The Examiner rejects claims 4 and 5, finding that the limitation "the transcript" lacks sufficient antecedent basis. Claim 4 has been amended such that it no longer refers to "the transcript," and claim 1 has been amended such that claim 5 has proper antecedent basis..

The Examiner has rejected to claims 4 and 5 as vague and indefinite, finding the metes and bounds of "lying within about" unclear. Claim 4 has been amended to recite an entirely different limitation and the original language of claim 4 is amended for clarity and incorporated into claim 1. Claim 5 has also been amended. The Examiner contends that there are two interpretations of this claim (that *at least one nucleotide* of the portion lay within 50 nucleotides of the translation initiation codon, and that *the entire portion* of the portion lay within 50 nucleotides of this region.) In the interests of facilitating prosecution, Applicants herein limit the claim to the narrower of the two interpretations but reserve the right to pursue further claim scope in an appropriate continuation or divisional. These amendments should now more accurately convey the limitation that the binding portion of the transcript is entirely within 50 nucleotides of the translation initiation codon. Support for this amendment is inherent in the language of the original claim.

The Examiner has rejected claims 15 and 16 as vague and indefinite, finding the metes and bounds of "the internucleosidic linkage" unclear. The Examiner was unclear as to whether applicants were specifically limiting the claims to one internucleosidic linkage by recitation in the singular or if more than one linkage was tolerated and all internucleosidic linkages meet the limitations of the

dependent claims. Applicants have amended claim 16 to clarify that one or more nucleosidic linkage is tolerated.

The Examiner further rejected claim 15 on the basis that the compounds are listed alternatively in the singular and plural. Without intending to limit the scope of the claim, applicants have amended claim 15 such that all compounds are referred to in the singular. At least one selected from the group may be used with the present invention.

The Examiner has pointed out that original claim 16 was vague and indefinite in that the metes and bounds of "the internucleosidic linkage is a phosphodiester linkage" was unclear because phosphodiester linkages are not nuclease resistant. Applicants agree, and have amended the claim. The claim has been amended such that the internucleosidic linkage referred to is the nuclease-resistant phosphorothioate linkage, and not a phosphodiester linkage. Claim 17 has now been amended making this rejection moot for claim 17.

The Examiner has rejected Claim 28 as lacking antecedent basis for the term "said composition being." Applicant has amended the claim to remove the word "being" such that there is now sufficient antecedent basis.

In light of the amendments set forth above, applicants respectfully submit that the rejections under 35 U.S.C. §112 have been overcome and should be withdrawn.

Claim Rejections - 35 USC §102

The Examiner has rejected claims 1-5 under 35 U.S.C. 102(b) as being anticipated by Kleisch et al. In light of the present amendments, applicants respectfully assert that this rejection has been overcome and should be withdrawn.

In response to both the 102 and 103 rejections set forth by the Examiner, claim 1 has been amended. Claim 1 now claims a composition for use in regulating hormones of a host comprising at least one antisense oligonucleotide that is complementary to the sequence of the FSHR gene, including the additional limitations as previously set forth in the original dependent claims 2, 3, 4, 8, and 13.

Newly amended claim 1 (incorporating the limitations of original claims 2, 3, 4, 8 and 13) now claims antisense oligonucleotides that comprise at least 8 nucleotides of SEQ ID NOs 1-4. Support for this is found at P.30, lines 12-14 and P.31, lines 4-6 of the specification. [1]

Newly amended claim 1 is not anticipated by Kleisch et al. Amended claim 1 includes additional limitations that are not taught by this reference. Claim 1 is now directed towards a composition having the following characteristics: 1) the antisense oligonucleotide is selected from the group consisting of deoxyribonucleosides, ribonucleosides, alpha-anomeric deoxyribonucleosides, alpha-anomeric ribonucleosides, and polyamide nucleic acids; 2) the antisense oligonucleotide is capable of forming a stable duplex with a portion of a FSHR transcript is lying within about 50 nucleotides from the translation initiation codon of the target nucleotide sequence; 3) the antisense oligonucleotide is specific for the FSHR gene in the ovarian granulosa cell of a human host; 4) the antisense oligonucleotide is an oligomer containing at least 8 nucleotide residues and is less than 60 nucleotides; and 5) comprises at least 8 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO:2, SEQ ID NO:3, and SEQ ID NO:4.. Of particular import, claim 1 now includes the limitation of being selected from the sequences as set forth in SEQ ID NOs 1-4. This language was originally found in claim 13, and was not rejected by the Examiner as anticipated under §102, or obvious under §103.

As a result of these amendments, none of the references cited by the examiner anticipate the claims. The primary reference relied on by the Examiner was the Kleisch reference. In light of the present amendments, Kleisch does not anticipate independent claim 1. Kleisch does not

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[1] At page 30, the specification reads: "The sequence of an antisense oligonucleotide according to the invention may be fully complementary to the DNA and/or mRNA sequence to be bonded. On the other hand, *the antisense oligonucleotide may also contain one or more nucleotides which are not complementary to the corresponding nucleotides of the sequence to be bonded*," emphasis added. At page 31, the specification reads: "The antisense compounds in accordance with this invention preferably comprise from about 8 to about 30 nucleobases." This is support for amendments to the claims which reflect that changes to SEQ ID Nos 1-4, and fragments of the SEQ ID Nos 1-4 having less than 28 nucleotides are within the original disclosure.

teach an antisense oligonucleotides specific for the FSHR gene that binds to a portion of the transcript lying within 50 nucleotides of the human FSHR gene translation initiation codon. To Applicant's knowledge, the transcript taught in Kleisch binds more than 50 nucleotides away from this region. Based on a Entrez PubMED BLAST search (provided by the National Center for Biotechnology Information, available online), it appears that the first of the Kleisch probes binds at a site 124 nucleotides away from the FSHR start codon. The second probe taught in Kleisch appears to bind at a site over 700 nucleotides away from the start codon. Therefore, the Kleisch reference does not teach this limitation of the claims.

Further, the oligonucleotides taught in Kleisch appear to encompass both FSHR sequence and sequence that provides a restriction site. The oligonucleotides were designed based on the human FSHR, encoding part of the extracellular domain of the receptor with the addition of an EcoRI and HindIII restriction site. (Kleisch at page R46, second full paragraph.) Thus, the Kleisch oligonucleotide comprises sequence that is complementary to the FSHR gene and a restriction site. The present invention claims oligonucleotides having sequence that is complementary to the FSHR gene, and does not include sequence for a restriction enzyme.

Finally, Kleisch does not teach the nucleotide sequences of SEQ ID Nos 1-4, which is now claimed in amended claim 1. Klesich also does not teach *at least 8 nucleotides* of SEQ ID Nos 1-4 which is the subject of claim 1. As a result, Kleisch cannot anticipate the independent claims as currently pending.

The Examiner also rejected claims 1-2 under 35 U.S.C. 102(b) as being anticipated by Slootstra and Roubos. The Examiner has read the Slootstra and Roubos reference to teach a composition comprising at least one antisense oligonucleotide that is a ribonucleoside complementary to a nucleotide sequence corresponding to a region overlapping the translation start codon. For this proposition, the Examiner has cited figure 1 in the reference. However, the Slootstra and Roubos reference does not concern oligonucleotides, but rather, *peptides* consisting of amino acids that correspond to the human FSH, and figure 1 of the reference discloses a schematic of the FSHR and a diagram of the sense and antisense peptides used in relation to the gene. (Note that AUU—the codon

shown in Figure 1—is only a start codon in prokaryotes.[2]) The Slootstra and Roubos reference does not disclose antisense oligonucleotide sequences (though Applicant appreciates that the peptides used were derived from the corresponding DNA sequence).

In addition to disclosing only peptides, and not oligonucleotides, the sequence corresponding to the peptides would not fall within applicant's amended claims. It appears that the amino acid closest to the start codon in the peptides taught by Slootstra and Roubos is at position 33. (See page 267, middle of first paragraph referring to synthetic peptide "TRDL.") This would be approximately 99 nucleotides downstream from the start codon. Applicant claims at least one antisense oligonucleotide that corresponds to a transcript of the FSHR corresponding to sequence lying within 50 nucleotides of the translation initiation codon. The sequence corresponding to the Slootstra and Roubos peptides appear not to meet this limitation.

The remaining claims depend from the first independent claim 1. As a result, none of the currently pending claims are anticipated under 35 U.S.C. § 102 for the above reasons, and the rejections set forth by the Examiner are overcome. The claims are now in condition for allowance.

Claim Rejections - 35 USC §103

The Examiner has rejected claims 1-12, 14-22 and 26-29 under 35 U.S.C. 103(a) as being unpatentable over Kleisch et al in view of Bennett and Cowsert and Baracchini et al and in view of Gromoll et al. Further, the Examiner rejected Claims 1-12 and 14-30 as being unpatentable over Kleisch et al. in view of Bennett and Cowsert and Baracchini et al and in view of Gromoll et al further in view of Baer et al and Zupi and Liang et al.

By amendment to the claims, these rejections have been overcome, and applicant respectfully submits that the rejection should be withdrawn. Claims 1-9, 15-19, and 28 have been amended. Independent claim 1 now has additional limitations that are not taught by the prior art cited by the Examiner. Specifically, claim 13 (which was not rejected by the Examiner as obvious or anticipated) has been added to amended claim 1, in addition to the limitations of claims 2, 3, 4, 7, and 8.

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[2] See http://en.wikipedia.org/wiki/Codon.

Given these amendments to the claims, the references cited by the Examiner can no longer be combined to teach the present invention as claimed. In particular, none of the references cited by the Examiner teach the oligonucleotide sequences in SEQ ID NOs 1-4 or a sequence directed to a portion of the transcript lying within 50 nucleotides of the start codon as now claimed by Applicant in independent claim 1. As such, applicant respectfully submits that the rejection under 35 U.S.C. §103 has been overcome and the rejection should be withdrawn. The claims are now in form for allowance.

CONCLUSION

In light of the amendments and remarks made herein, it is respectfully submitted that the claims currently pending in the present application are in form for allowance. Accordingly, reconsideration of those claims, as amended herein, is earnestly solicited. Applicants encourage the Examiner to contact their representative, Stephen R. Albainy-Jenei at (513) 651-6839 or salbainyjenei@fbtlaw.com.

The Commissioner for Patents is hereby authorized to charge any deficiency or credit any overpayment of fees to Frost Brown Todd LLC Deposit Account No. 06-2226.

Respectfully submitted,
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